# CHARGE TO EXTERNAL PEER REVIEW PANEL FOR PERCHLORATE TOXICITY

## I. REVIEW OF INDIVIDUAL STUDIES INITIATED SINCE MAY 1997

For each study report assigned to you as a primary or secondary reviewer, please respond to the following questions:

1. Please comment on the strengths and weaknesses of the experimental design of the study. Are the questions being investigated in each study clearly identified? Are they important to enhancing the toxicological (ecotoxicological) characterization of perchlorate? Is the study design appropriate to answer the questions? Discuss all limitations in experimental design that would affect the ability to interpret the significance of study results. Also indicate areas in which insufficient information has been provided on the experimental design.

2. Please comment on any limitations in the conduct of the study which could decrease the relevance of study findings. For example, were the studies conducted in accordance with Good Laboratory Practices? Were there occurrences that necessitated a change in the protocol during the course of the study? If so, what impact did these changes have on the findings?

3. Please comment on the strengths and weaknesses of the statistical methodology(ies) used to evaluate study findings. What other statistical analyses, if any, should be performed?

4. Please comment on the strengths and weaknesses of the presentation of the investigations in the study report. Were sufficient data presented in the report and its appendices to confirm the findings presented in the report? Are the conclusions of the report supported by the data? Please explain.

5. Overall was the study as designed, performed and reported of sufficient quality for use for hazard characterization purposes? If so, indicate the extent to which it can be used for characterizing human health/ecotoxicological effects of ammonium perchlorate and the perchlorate ion. Do the findings provide information relevant to evaluating the sensitivities of specific subpopulations of exposed individuals and attendant effects (e.g., infants, hypothyroid individuals)?

6. For the studies that are not yet complete, are sufficient data available on experimental design, conduct and interim observations to derive meaningful conclusions? If so, what caveats, if any, should be placed on these conclusions? Or should all data from the study be evaluated following the conclusion of the study and development of the final study report?

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II. REVIEW OF TOXICOLOGICAL REVIEW DOCUMENT

A. EFFECTS OF CONCERN TO HUMAN HEALTH (all reviewers except Dr. Cardwell)

Please comment on the adequacy of the Toxicological Review document in presenting and evaluating the existing toxicology data base on ammonium perchlorate and the perchlorate ion relevant to effects on human health.

1. Have the key aspects of the protocols, conduct and results of each toxicology study been adequately described in the Toxicological Review document? Where limitations exist in study reports or published papers, have they been appropriately discussed in the Toxicological Review document? In what ways might the discussion of studies be improved?

2. Indicate the strengths and weaknesses of the analyses performed on the data in the Toxicological Review document first of specific toxicological studies and then of the overall toxicology data base on perchlorate. Has the document adequately evaluated the results of all relevant studies and the biological significance of the entire data base? Where inconsistencies appear to exist in the findings relevant to the hypothalamic-pituitary-thyroid axis within and between studies, does the document adequately address such inconsistencies? Enumerate specific improvements that should be made, if any.

3. Authors of the Toxicological Review document provided statistical analyses beyond those contained in the original study reports of recently completed studies. Where these statistical analyses were performed, were the appropriate methodologies used? Did they add to the overall understanding/relevance of the studies? Were the appropriate endpoints and/or time points used? Please explain.

4. Note any relevant references that have not been cited in the Toxicological Review document and their relevance to hazard characterization of ammonium perchlorate and the perchlorate ion.

B. ECOTOXICOLOGICAL EFFECTS OF CONCERN (Dr. Cardwell)

Please comment on the adequacy of the Toxicological Review document in presenting and evaluating the existing data base of ecotoxicological effects of ammonium perchlorate and the perchlorate ion.

1. Have the key aspects of the protocols, conduct and results of each study of ecotoxicological effects been adequately described in the Toxicological Review

document? Where limitations exist in study reports or published papers, have they been appropriately discussed in the Toxicological Review document? In what ways might the discussion of studies be improved?

2. Indicate the strengths and weaknesses of the analyses performed on the data from individual studies of ecotoxicological effects and then of the overall data base on ecotoxicological effects of perchlorate. Has the document adequately evaluated the results of all relevant studies and the biological significance of the entire data base?

3. Note any relevant references on ecotoxicological effects of ammonium perchlorate or other perchlorate salts that have not been cited in the Toxicological Review document and their relevance to the characterization of ecotoxicological effects of these compounds.

C. ADDITIONAL ISSUES PERTAINING TO THE TOXICOLOGICAL REVIEW DOCUMENT (all peer reviewers)

1. Are there other sections of the document that could be improved? Please specify and note the revisions that would improve the document.

2. Is the document as currently written useful for the purpose of characterizing the human health/ecotoxicological effects of ammonium perchlorate and the perchlorate ion? If not, specify the nature and extent of changes that are needed.

## III. HAZARD CHARACTERIZATION

A. DEVELOPMENT OF REFERENCE DOSE (RfD) (all reviewers except Dr. Cardwell)

See the attached summary of the EPA guidelines for evaluating noncancer health effects of environmental chemicals through the development of reference doses (RfDs) and for evaluating carcinogenic effects through the development of cancer potency factors.

1. The Toxicological Review document developed no observed adverse effect levels (NOAELs) and/or lowest observed adverse effect levels (LOAELs) for most of the studies discussed in the document. Are the individual NOAELs/LOAELs appropriate given the totality of data from each study? Please explain.

2. It is general EPA policy to develop estimates of non-cancer toxicities of environmental chemicals by using the results on the most sensitive toxic endpoint from the group of toxicology studies that have been performed on the chemical.

This serves as the basis for the reference dose(RfD), an estimate of a daily lifetime exposure without risk of deleterious noncancer effects during a lifetime. Given that all available data indicate that the thyroid organ is the most sensitive organ for perchlorate toxicity, it is important to assess the internal consistency of the overall data base. Comment on the use of a single study or the totality of data on thyroid toxicology as the basis for establishing an RfD.

3. The approach used in the Toxicological Review document for developing an RfD for perchlorate was to identify the principal study as the neurodevelopmental toxicity study in rats and the critical effect as the decrease in follicular lumen size and follicular cell hyperplasia observed in pups on postnatal day 5 at the 0.1 mg/kg/day dose. Is this the appropriate selection? Is the designation of the 0.1 mg/kg/day dose as a "minimal" LOAEL an appropriate choice based upon the totality of the data? If not, specify a more appropriate approach to developing an RfD based upon the current toxicology data base.

4. The EPA position, as stated in the document entitled "Assessment of Thyroid Follicular Cell Tumors," is that in the absence of chemical-specific data, humans and rodents are presumed to be equally sensitive to thyroid cancer due to thyroid-pituitary disruption. This is considered to be a public health protective position where thyroid-pituitary disruptions are the sole mode of action, because rodents appear to be more sensitive to this carcinogenic mode of actions than humans. The available data base on the perchlorate ion indicates that disruption of the thyroid-pituitary axis is the most sensitive endpoint. Further, long-term treatment with perchlorate induced benign thyroid tumors in rats. Moreover, perchlorate appears not to be genotoxic based upon available data. Given the above EPA position and the toxicity data base on perchlorate, is the choice of an uncertainty factor of 3 for extrapolating potential differences in iodide inhibition between rodents and humans appropriate in the derivation of the RfD? If not, what should the uncertainty factor be for interspecies extrapolation?

5. Additional uncertainty factors of 3 each were used to account for using a minimal LOAEL as opposed to a NOAEL and to partially address intrahuman variability in pharmacodynamics, for data base deficiencies, and for accounting for intrahuman variation (sensitive subpopulations) in iodide uptake inhibition. Identify the strengths and limitations of using 3 as the value for each of these uncertainty factors. Would other values (e.g., 10 or 1) have been more appropriate? If so, specify those values and the reasons for their selection.

6. The Toxicological Review document concludes that the "RfD" is actually a harmonized oral human health risk estimate that will be protective for both

noncancer health effects and cancer endpoints of perchlorate ion since the RfD is based upon reversible effects observed at dose levels below those at which thyroid tumors or neurodevelopmental effects were induced in the rat studies. Do the existing data support this position? Please explain.

B. ECOTOXICOLOGICAL ASSESSMENT (Dr. Cardwell)

1. Comment on whether the goals and objectives of this ecological screening analysis have been adequately described and to what extent these have been met.

2. Does the analysis support the summary and conclusions presented? Are relevant and important aspects of uncertainty are addressed sufficiently? Which aspects are not, and how could the discussion be improved?

3. Comment on whether the assays selected for evaluation in the ecological screening analysis can be reasonably expected to identify potential ecological effects of concern.

## IV. FURTHER TESTING NEEDS FOR PERCHLORATE

A. TOXICOLOGICAL TESTING (all members of the peer review panel except Dr. Cardwell)

1. Were the experimental designs of the toxicity studies undertaken since May 1997 adequate to identify the potential hormone disrupting effects on development and reproductive performance due to thyroid function perturbations at low exposure levels? If not, specify more appropriate protocols.

2. Identify additional toxicology studies that would lead to a more complete toxicological characterization of ammonium perchlorate and the perchlorate ion. Provide information on the protocols that should be utilized.

3. Comment on the potential value added to these analyses by the development of a physiologically-based pharmacokinetic model to address species differences in inhibition of iodide uptake, perchlorate kinetics, and subsequent perturbations of the hypothalamic-pituitary-thyroid axis.

B. ECOTOXICOLOGICAL TESTING (Dr. Cardwell)

1. Will the additional ecotoxicological studies currently underway be sufficient to

characterize the ecotoxicological potential of ammonium perchlorate and the perchlorate ion? If not, explain what data needs will be unmet and describe further studies that should be considered, present the rationale for the studies, and provide overviews of the types of experimental designs that will be needed.